BD X-12591

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 535 722 A1**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: **92202082.1**

(22) Date of filing: **08.07.92**

(51) Int. Cl.5: **C07D 409/04**, C07D 405/04, C07D 401/04, A61K 31/33, A61K 31/44

(30) Priority: **15.07.91 EP 91201855**

(43) Date of publication of application: **07.04.93 Bulletin 93/14**

(84) Designated Contracting States: **AT BE CH DE DK ES FR GB GR IT LI LU NL PT SE**

(71) Applicant: **DUPHAR INTERNATIONAL RESEARCH B.V**
C.J. van Houtenlaan 36
NL-1380 AC Weesp(NL)

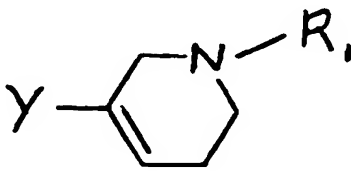
(72) Inventor: **Hulkenberg, Antonius**
c/o OCTROOIBUREAU ZOAN B.V. P.O. Box 140
NL-1380 AC Weesp(NL)

Inventor: **van Charldorp, Karin J.**
c/o OCTROOIBUREAU ZOAN B.V. P.O. Box 140
NL-1380 AC Weesp(NL)
Inventor: **van Hes, Rolf**
c/o OCTROOIBUREAU ZOAN B.V. P.O. Box 140
NL-1380 AC Weesp(NL)
Inventor: **van Wijngaarden, Ineke**
c/o OCTROOIBUREAU ZOAN B.V. P.O. Box 140
NL-1380 AC Weesp(NL)

(74) Representative: **Muis, Maarten et al**
OCTROOIBUREAU ZOAN B.V. P.O. Box 140
NL-1380 AC Weesp (NL)

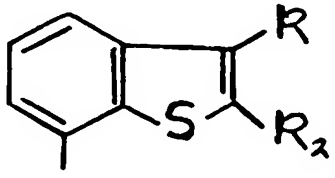
(54) **3,4-Dehydropiperidine derivatives.**

(57) The invention relates to a group of new 3,4-dehydropiperidine derivatives of the formula



wherein

R_1 is a hydrogen atom or an alkyl group having 1-3 carbon atoms;
Y is a group of the general formula 2



(2)

EP 0 535 722 A1

wherein

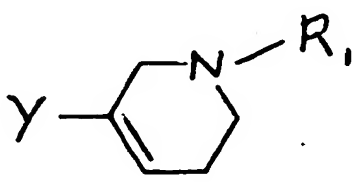
R_2 is a group of the formula $-(CH_2)_n-C(=X)-NR_3R_4$, $-(CH_2)_n-SO_2-NR_3R_4$, $-(CH_2)_n-NR_5-C(=X)-R_6$ or $-(CH_2)_n-NR_5-SO_2-R_6$, wherein R_3, R_4 and R_5 independent of each other represent hydrogen or alkyl (1-3C), R_6 is alkyl (1-3C), X represents O or S; n is 0-4, and

R is hydrogen or alkyl (1-3C).

These compounds have interesting serotonin-1-like (partial) agonistic activity and can be used for the treatment of migraine.

The invention relates to new 3-substituted 3,4-dehydropiperidine derivatives having anti-migraine activity.

It was found that 3,4-dehydropiperidine derivatives of the general formula 1

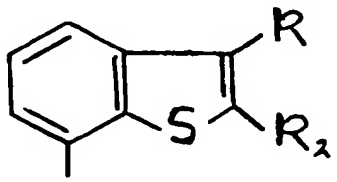


(1)

wherein

R_1 is a hydrogen atom or an alkyl group having 1-3 carbon atoms;

Y is a group of the general formula 2



(2)

wherein

R_2 is a group of the formula $-(CH_2)_n-C(=X)-NR_3R_4$, $-(CH_2)_n-SO_2-NR_3R_4$, $-(CH_2)_n-NR_5-C(=X)-R_6$ or $-(CH_2)_n-NR_5-SO_2-R_6$, wherein R_3, R_4 and R_5 independent of each other represent hydrogen or alkyl (1-3C), R_6 is alkyl (1-3C), X represents O or S; and n is 0-4;

R is hydrogen or alkyl (1-3C),

have serotin 1-like (partial) agonistic activity which can be used for the treatment of migraine.

The so-called prodrugs and acid addition salts of the compounds of formula 1 also belong to the invention. Prodrugs are to be understood to mean derivatives of these compounds, which are inactive as such but from which, after removal of an easily removable group. i.e. an ester group or an ether group, an active compound of formula 1 is obtained.

When a chiral center is present both the different enantiomers and the racemate belong to the invention.

Examples of suitable acids with which the compounds according to the invention can form pharmaceutically acceptable salts are hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, organic acids, like citric acid, fumaric acid, tartaric acid, acetic acid, maleic acid, benzoic acid, p-toluene sulphonic acid, methane sulphonic acid and the like.

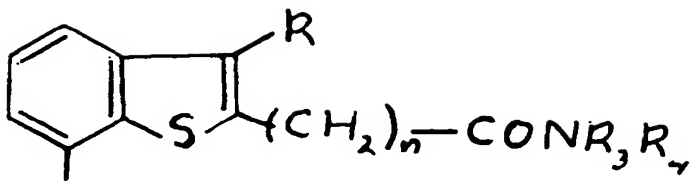
The compounds of the invention show an interesting serotonin 1-like (partial) agonistic activity. Compounds having this activity are potential antimigraine drugs.

This activity against migraine is determined by means of the following test model. Serotonin causes via stimulation of 5-HT_1-like receptors a concentration-dependent contraction of isolated strips of A. basilaris of the pig. (Naunyn Schmiedeberg's Arch. of Pharmacol. 1990, suppl to vol. 341, R 89). The compounds according to the invention are active in dosages which as a rule are between 0.1 and 100 mg/kg after oral administration.

The compounds can be brought into a form suitable for humane application in the conventional manner, that is to say, formulated to compositions suitable for this purpose and to be preferable administered orally.

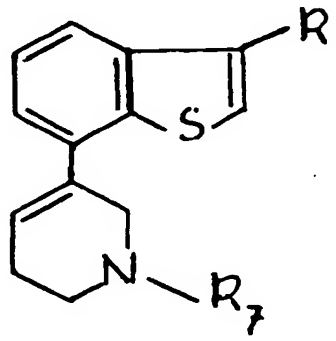
The new compounds according to the invention can be obtained in a manner known for the synthesis of analogous compounds.

Compounds having formula (1) wherein R_1 has the above meanings and Y is a group of formula 3



(3)

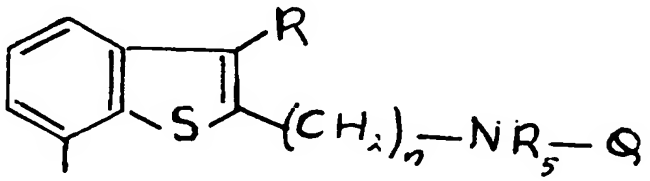
wherein n, R, R_3 and R_4 have the above meanings can be obtained, for example, by reacting a compound of formula 4



(4)

wherein R_7 is alkyl(1-3C) or benzyl with butyllithium, followed a) by a reaction with CO_2, and conversion of the carboxylate so-obtained into an amide, or b) by a reaction with an alkylisocyanate, or c) by alkylation with a suitable functionalised bromoalkylderivative.

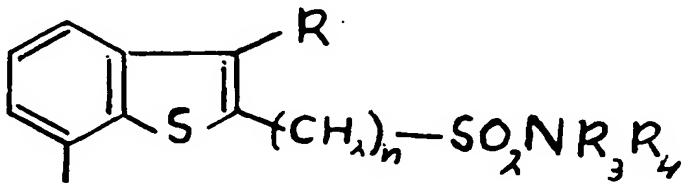
Compounds having formula 1 wherein R_1 has the above meanings and Y is a group having formula 5



(5)

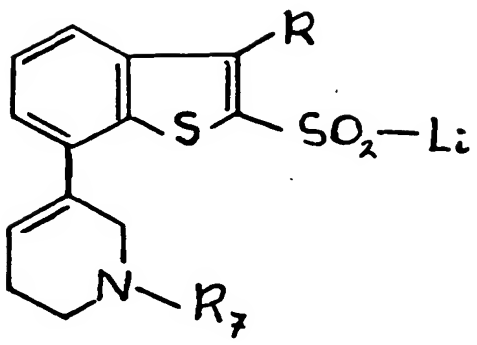
wherein n, R and R_5 have the above meanings, and Q is a group of the formula $-(C=X)-R_6$ or $-SO_2-R_6$, in which groups X, and R_6 have the above meanings, can be prepared by reduction of a compound obtained according to a), b) or c) above, with $LiAlH_4$ giving the corresponding amines, followed by reaction with a suitable acylating or sulfonylating agent.

Compounds of the formula 1 wherein R_1 has the above meanings and Y is a group of formula 6



(6)

wherein n, R, R_3 and R_4 has the meaning given above, can be prepared from the corresponding lithium sulfinate of the formula 7



(7)

wherein R has the meaning given above, R_7 is alkyl(1-3C) or benzyl according to methods described in Synthesis, (1986), 1031; Synthesis, (1986), 852, and Bull. Chem. Soc. Jpn, 43, (1970), 1256.

To obtain the final compounds according to these methods wherein R_1 is hydrogen, the protective benzyl group has to be removed by methods known for debenzylation.

The invention will now be described in greater detail with references to the ensuing specific examples.

EXAMPLE I

2-(N-methylcarbamoyl)-7-(3,4-dehydropiperidyl-3)-benzo[b]thiophene

15.25 g (50 mmol) of 7-(N-benzyl-3,4 dehydropiperidyl-3)-benzo[b]thiophene (which can be obtained as described in EP 0398413) is dissolved in 150 ml of dry tetrahydrofuran. The solution is cooled at -70 C. After adding 1.1 equivalent of butyllithium in hexane the reaction mixture is stirred for 30 minutes, after which a solution of methylisocyanate (6 ml) in tetrahydrofuran (50 ml) is added dropwise. The mixture is stirred for 30 minutes at -70 C, and overnight at room temperature. The reaction mixture is poured into 500 ml of water, and extracted with ethylacetate (3 x 200 ml). The combined organic layers are washed with water (2 x 200 ml), with brine (200 ml) dried and evaporated to dryness.

After purification by chromatografy (silicagel/ethylacetate:hexane = 1:2). 2-(N-methylcarbamoyl)-7-(N-benzyl-3,4 dehydropiperidyl-3)-benzo[b]thiophene is obtained.

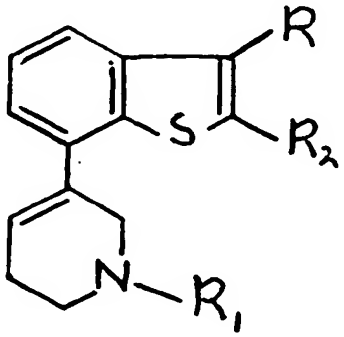
A solution of the so-obtained compound (9.6 g) in 1,2-dichloroethane (100 ml) is cooled to 0 C.

After adding 5.8 ml of 1-chloroethylchloroformate (53 mmol) the reaction mixture is heated to reflux temperature for two hours.

After evaporation of the benzylchloride, 100 ml of methanol is added and the reaction mixture is stirred at room temperature for 16 hours.

The solvent is evaporated and the residue is purified by chromatografy (silicagel/ethylacetate:methanol:ammonia = 95:4.5:0.5. Yield 1.7 g of 2-(N-methylcarbamoyl)-7-(3,4-dehydropiperidyl-3)-benzo[b]thiophene. M.p. 173 C (free base) ; 202 C (fumarate).

The following compounds have also been prepared:



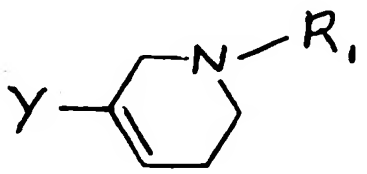
EXAMPLE	R	R_1	R_2	melting point (C)
II	H	H	$-CON(CH_3)_2$	foam (fumarate)
III	H	H	$-CH_2CON(CH_3)_2$	foam (fumarate)
IV	H	H	$-CH_2NH-SO_2CH_3$	foam (free base)
V	H	H	$-CH_2NH-COCH_3$	foam (fumarate)
VI	H	H	$-CONH_2$	292 (HCl)
VII	H	H	$-SO_2NH_2$	>300 (HCl)
VIII	H	H	$-SO_2NHCH_3$	191 (HC1)
IX	CH_3	H	$-CONHCH_3$	236 (HC1)

The compounds of Examples II to V were obtained as a foam. These compounds have been identified by means of ^{1}H-NMR spectra, among others of the protons in substituent R_2:

Example	Spectrum of group R_2
II	σ = 3.24(3H,bs,N-CH_3); 3.08(3H,bs,N-CH_3)
III	σ = 4.04(2H,s,-CH_2-); 3.09(3H,s,N-CH_3); 2.88(3H,s,N-CH_3)
IV	σ = 4.45(2H,s,-CH_2); 2.90(3H,s,SO_2-CH_3)
V	σ = 4.51(2H,d,-CH_2-; 8.59(1H,t,NH-CO); 1.89(3H,s,-CO-CH_3)
s = singlet d = doublet t = triplet bs = broad singlet	

Claims

1. 3,4-dehydropiperidine derivatives of the formula

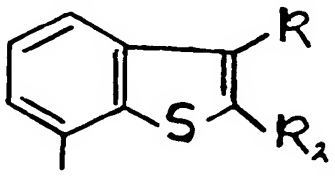


(1)

wherein

R_1 is a hydrogen atom or an alkyl group having 1-3 carbon atoms;

Y is a group of the general formula 2



(2)

wherein

R_2 is a group of the formula $-(CH_2)_n-C(=X)-NR_3R_4$, $-(CH_2)_n-SO_2-NR_3R_4$, $-(CH_2)_n-NR_5-C(=X)-R_6$ or $-(CH_2)_n-NR_5-SO_2-R_6$, wherein R_3, R_4 and R_5 independent of each other represent hydrogen or alkyl (1-3C), R_6 is alkyl (1-3C), X represents O or S; and n is 0-4;

R is hydrogen or alkyl (1-3C),

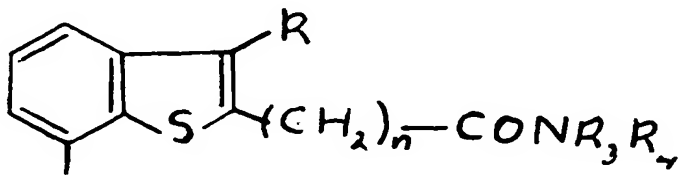
and prodrugs and pharmaceutically acid addition salts thereof.

2. A pharmaceutical composition which comprises a 3,4-dehydropiperidine derivative as the active substance, characterized in that the composition comprises at least one compound as claimed in claim 1.

3. A method of preparing a composition having antimigraine activity, characterized in that a compound as claimed in claim 1 is brought into a form suitable for administration.

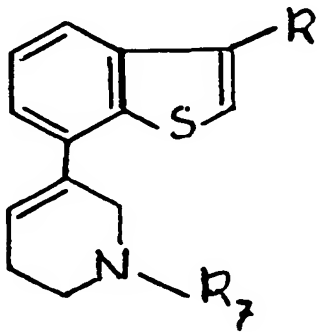
4. A method of preparing 3,4-dehydropiperidine derivatives, characterized in that compounds as claimed in claim 1 are prepared according to methods known for the synthesis of analogous compounds.

5. A method as claimed in claim 4, characterized in that a compound of formula 1 is prepared wherein R_1 has the meaning given in claim 1 and Y is a group of formula 3



(3)

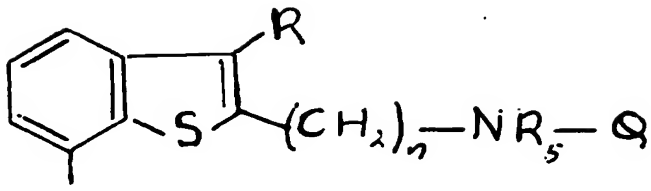
wherein n, R, R_3 and R_4 have the meanings given in claim 1, by reacting a compound of the formula 4



(4)

wherein R_7 is alkyl(1-3C) or benzyl, with butyllithium, followed a) by a reaction with CO_2, and conversion of the carboxylate so-obtained into an amide, or b) by a reaction with an alkylisocyanate, or c) by alkylation with a suitable functionalised bromoalkylderivative, and optional removal of the protective benzyl group R_7.

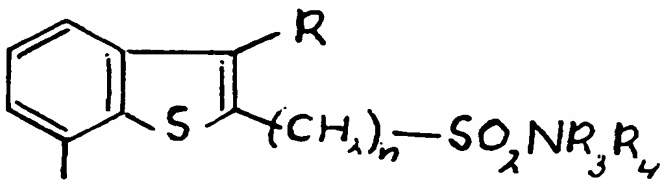
6. A method as claimed in claim 4, characterized in that a compound of formula 1 is prepared wherein R_1 has the meaning given in claim 1, and Y is a group of formula 5



(5)

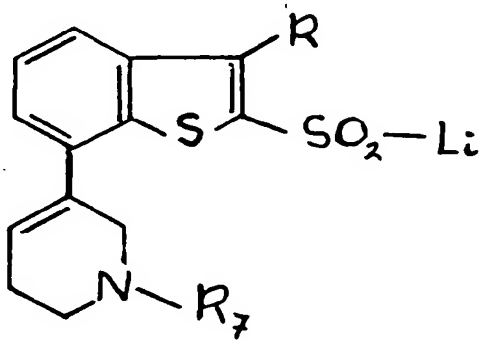
wherein n, R and R_5 have the meanings given in claim 1, and Q is a group of the formula -(C=X)-R_6 or -SO_2-R_6, in which groups X, R_3, R_4 and R_6 have the meanings given in claim 1, by reduction of a compound obtainable according to the method of claim 5a, b or c with $LiAlH_4$, followed by reaction with a suitable acylating or sulfonylating agent, and, if present, removal of the protective benzyl group R_7.

7. A method as claimed in claim 4, characterized in that a compound of formula 1 wherein R_1 has the meaning given in claim 1, and Y is a group of formula 6



(6)

wherein R, R_3, R_4 and n have the meanings given in claim 1 is prepared in a manner known per se from a lithium sulfinate of formula 7



(7)

wherein R has the meaning given in claim 1, R_7 is alkyl(1-3C) or benzyl, and, if present, removal of the protective benzyl group R_7.

8. A method of treating migraine, characterized in that a compound as claimed in claim 1 is used.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 20 2082

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 021 924 (ROUSSEL-UCLAF) * the whole document * ---	1-4,8	C07D409/04 C07D405/04 C07D401/04
A	GB-A-2 056 435 (CIBA-GEIGY A.G.) * the whole document * ---	1	A61K31/33 A61K31/44
A	EP-A-0 303 507 (GLAXO GROUP LIMITED) * abstract; page 2, lines 54-60; claims 1, 11, 13; formula II in claim 17 * ---	1,8	
D,A	EP-A-0 398 413 (DUPHAR INTERNATIONAL RESEARCH B.V) * page 1, line 1 - page 5, line 52; claims; example II * -----	1-8	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)
C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	24 SEPTEMBER 1992	B. Paisdor

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)